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Carboplatin and Etoposide in Heavily Pretreated Patients with Progressive High-Grade Glioma

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Abstract: BACKGROUND Treatment of recurrent anaplastic glioma and glioblastoma remains a particular challenge in neurooncology. The lack of controlled trials results in poor evidence for all therapeutic options. Upon recurrence, many patients are treated with bevacizumab or one of the frequently used nitrosoureas such as lomustine. However, patients who still present in overall good condition after failure of multiple lines of therapy may ask for additional therapy. **METHODS** Here, we report our experience with the use of carboplatin in combination with etoposide as fourth- or fifth-line therapy in patients with progressive high-grade glioma. **RESULTS** The median Karnofsky performance status at the beginning of treatment was 80%. The median progression-free survival (PFS) was 2.5 months. PFS at 6 months was 0%. Administration of carboplatin and etoposide was associated with grade 3 or 4 hematotoxicity in 8 of 12 patients. **CONCLUSION** Carboplatin in combination with etoposide has an unfavorable risk-benefit profile in heavily pretreated glioma patients.

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Carboplatin and etoposide in heavily pre-treated patients with progressive high-grade glioma

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Running title: Carboplatin/etoposide in high-grade gliomas

Key words: glioblastoma, high-grade glioma, carboplatin, etoposide, VP-16

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Abstract

Background: Treatment of recurrent anaplastic glioma and glioblastoma remains a particular challenge in neurooncology. The lack of controlled trials results in poor evidence for all therapeutic options. At recurrence, many patients are treated with bevacizumab or one of the frequently used nitrosoureas such as lomustine. However, patients who still present in overall good condition after failure of multiple lines of therapy may ask for additional therapy.

Methods: Here, we report our experience with the use of carboplatin in combination with etoposide as fourth- or fifth-line therapy in patients with progressive high-grade glioma.

Results: Median Karnofsky performance status at the beginning of treatment was 80%. Median progression-free survival (PFS) was 2.5 months. PFS at 6 months was 0%. Administration of carboplatin and etoposide was associated with grade III or IV hematotoxicity in 8 of 12 patients.

Conclusion: Carboplatin in combination with etoposide has an unfavourable risk-benefit profile in heavily pre-treated glioma patients.

Introduction

First-line treatment of patients with anaplastic glioma and glioblastoma, also referred to as high-grade gliomas, has been largely standardized and includes radiation therapy and the alkylating agent temozolomide. Whether these treatment modalities are used in a combined approach or rather sequentially depends on the WHO grade, age as well as molecular markers such as the methylation status of the O⁶-methylguanine DNA methyltransferase (*MGMT*) gene promoter [1-3]. In contrast, treatment is much less standardized when the tumor recurs [4]. The anti-angiogenic agent bevacizumab has been approved for recurrent glioblastoma in the US but not in most European countries [5]. Other treatment options which are frequently used include re-resection [6], the administration of nitrosoureas such as lomustine [7-10], re-challenge with temozolomide [11] and numerous experimental drugs [12]. In general, these treatment options show limited activity. The situation is particularly challenging in patients suffering from repeated relapses who present in sustained good performance status asking for further therapy. Here we report our institutional experience with the combination of carboplatin and etoposide in heavily pre-treated patients with malignant gliomas at third or fourth tumor progression.

Patients and methods

We retrospectively reviewed the tumour board proceedings from 2010-2013 and identified 12 patients with recurrent high grade glioma treated with carboplatin ($240 \text{ mg/m}^2 \text{ d1}$) and etoposide ($100 \text{ mg/m}^2 \text{ d2 and d3}$) q 4 weeks following multiple prior therapies. All patients had magnetic resonance imaging (MRI) every 8-12 weeks or in the case of clinical deterioration. MRI was evaluated according to Response Assessment in Neuro-Oncology (RANO) criteria [13]. Progression-free survival (PFS) was determined from the date of treatment start on salvage carboplatin and etoposide therapy until the date of further progression according to the Kaplan-Meier method. Overall survival (OS) was calculated from the initiation of carboplatin and etoposide treatment until death. Total OS was determined from the date of initial surgery to death.

Results

Of the 12 patients, 8 had been diagnosed with glioblastoma, 3 with anaplastic astrocytoma and one patient with anaplastic oligodendroglioma. All patients had third or fourth tumor recurrence when treatment with carboplatin/etoposide was initiated. The median age at diagnosis was 50 years (range 37 – 68 years) with a preponderance of males (8 males, 4 women). Following initial surgery, further therapy lines consisted of radiation therapy (RT) alone (n=3; anaplastic astrocytoma), RT with concomitant and adjuvant chemotherapy with TMZ (n=7; glioblastoma), RT in combination with temsirolimus (n=1; EORTC 26082; NCT01019434; glioblastoma). One patient received no adjuvant therapy following surgery because of the initial diagnosis of a WHO grade II oligodendroglioma. Upon progression to an anaplastic glioma after 22 months, re-resection was performed with subsequent RT. In the other patients, second line therapy comprised re-resection followed by RT, re-exposure to TMZ or bevacizumab in combination with ornatuzumab/placebo (Genentech GO27819; NCT01632228). Patients not undergoing re-resection (n=7) received temozolomide or bevacizumab alone or in combination with RO5323441 [14]. Depending on pre-treatment, third and fourth line therapy consisted of TMZ, lomustine, bevacizumab alone or bevacizumab in combination with TMZ or lomustine. Carboplatin in combination with etoposide was administered as fourth line therapy in 3 patients and as fifth line therapy in nine.

Detailed patient characteristics are summarized in Table 1. At the time of initiation of carboplatin and etoposide, most patients presented in good overall condition with a median KPS of 80 % and only 4 out of 12 patients requiring steroid administration. Treatment with carboplatin and etoposide was only moderately tolerated and CTCAE grade III and IV hematotoxicity occurred in 67 % of the patients. Four patients

received granulocyte colony stimulating factor treatment and antibiotic prophylaxis for prolonged neutropenia.

The median PFS of patients receiving etoposide-based salvage therapy was 2.5 months. We did not record any complete or partial responses and PFS at 6 months was 0%. Median OS (mOS) after initiation of carboplatin/etoposide was 3.3 months (Figure 1). mOS from initial diagnosis was 21.7 months.

Discussion

There is no standard of care of patients with recurrent high-grade gliomas. Various drugs and regimens have been examined but no standard has been established so far [15]. Patients who experience repeated tumor progression may present with reduced KPS which does not allow for further tumor-specific therapy, but rather requires a change to best supportive care. However, a considerable number of patients are still in good KPS even after failure of multiple prior therapy lines. Here, we explored the combination of carboplatin and etoposide in patients with third or fourth recurrence of a high-grade glioma. Although only a limited number of patients was examined, our results do not point to a clinically relevant activity of such treatment. In contrast, we observed significant toxicity, associated with impaired quality of life which required hospitalisation of some patients.

Platinum-based antineoplastic agents alone or in combination with other drugs have been used for the treatment of gliomas for at least 2 decades [16, 17]. A rather intense regimen, including ifosfamide, carboplatin and etoposide (ICE) was administered to patients with high-grade glioma at second or third tumor recurrence [18]. Similarly to our findings, no complete or partial responses were observed. In contrast, promising activity of this regimen was reported in patients with first tumor recurrence with a PFS-6 of 35 % and median OS of 10.7 months from the beginning of ICE [19]. Activity has also been reported for carboplatin and etoposide in patients with recurrent high-grade glioma after initial surgical resection followed by radiation therapy and no prior chemotherapy with a PFS-6 of 20 % in a phase II study including 30 patients [20].

Our analysis suggests that the activity of carboplatin and etoposide in heavily pre-treated patients with high-grade glioma is low which may be partially explained by the

fact that all but one patient had received prior anti-angiogenic treatment with bevacizumab which may have precluded benefit from the drugs administered afterwards [21, 22]. Instead, severe toxicity was observed which may also reflect residual effects of multiple lines of previous therapy in all patients. Similar to previous studies, we used carboplatin at a dose of 240 mg/m^2 on day 1 [23]. *Area under the curve* (AUC)-based dosing (“Calvert formula”) may represent a more suitable way to define the best dose of carboplatin in terms of activity and tolerability. Still, because of its lacking activity and negative impact on quality of life, the combination of carboplatin and etoposide cannot be recommended as a routine salvage treatment. Thus, novel treatment approaches for patients with recurrent gliomas are urgently needed and should be in the focus of future clinical trials.

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Table 1. Patient characteristics

		Number of patients	Percentage [%]
Age (years)	Median	50	
	Range	37 - 68	
Sex	Male	8	67
	Female	4	33
Toxicity of carboplatin / etoposide	grade 3 / 4 leukopenia and neutropenia	8	67
	Treatment with G-CSF for prolonged neutropenia	4	33
KPS at initiation of carboplatin and etoposide			
	100	0	0
	90	5	42
	80	6	50
	70	1	8
Number of lines of chemotherapy prior to carboplatin/etoposide treatment	1	1	8
	3	5	42
	4	6	50
Steroid use at initiation of carboplatin and etoposide	No	8	67
	yes	4	33
MGMT status	methylated	2	17
	unmethylated	4	33
	undetermined	6	50
IDH1 status	mutated	1	8
	wild type	9	75
	undetermined	2	17

Figure legend

Progression-free and overall survival of 12 patients with third or fourth progression of a high-grade glioma treated with carboplatin and etoposide as fourth or fifth line therapy (OS with 2 censored cases because still alive at the time of closure of the database).